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PARKINSON'S 101

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What is Parkinson's disease?
Parkinson's disease is a chronic, degenerative neurological disorder that affects one in 100 people over age 60. While the average age at onset is 60, people have been diagnosed as young as 18. There is no objective test, or biomarker, for Parkinson's, so the rate of misdiagnosis can be relatively high, especially when the diagnosis is made by a non-specialist. Estimates of the number of people living with the disease therefore vary, but recent research indicates that at least one million people in the United States, and more than five million worldwide, have Parkinson's.

Parkinson's disease was first characterized extensively by an English doctor, James Parkinson, in 1817. Today, we understand Parkinson's to be a disorder of the central nervous system that results from the loss of cells in various parts of the brain, including a region called the substantia nigra. The substantia nigra cells produce dopamine, a chemical messenger responsible for transmitting signals within the brain that allow for coordination of movement. Loss of dopamine causes neurons to fire without normal control, leaving patients less able to direct or control their movement. Parkinson's is one of several diseases categorized by clinicians as movement disorders.

What range of symptoms are part of Parkinson's disease?
People are generally most familiar with the motor symptoms of Parkinson's disease, as they are the most evident signs of the disease from the outside. These symptoms, which are also called the "cardinal" symptoms of PD, are resting tremor, slowness of movement (bradykinesia), postural instability (balance problems) and rigidity. Some other physical symptoms such as gait problems and reduced facial expression are also of note. These are due to the same discoordination of movement that causes the better-known tremor and slowness.

There is also increasing recognition of the importance of other symptoms of PD that are sometimes called "non-motor" or "dopamine-non-responsive" symptoms. While neither of these terms is ideal, these symptoms are common and can have a major impact on people with PD. For example, cognitive impairment, ranging from mild memory difficulties to dementia, and mood disorders, such as depression and anxiety, occur frequently. Also common are sleep difficulties, loss of sense of smell, constipation, speech and swallowing problems, unexplained pains, drooling, constipation, and low blood pressure when standing.

Parkinson's symptoms manifest differently in different patients. Many patients experience some symptoms and not others, and even the pace at which the disease worsens varies on an individual basis.

How is Parkinson's disease diagnosed?
The cardinal symptoms of Parkinson's (resting tremor, slowness of movement (bradykinesia), balance problems (postural instability), and rigidity are the hallmarks of the disease. These symptoms, which often appear

gradually yet with increasing severity, are usually what first bring patients to a neurologist for help. Typically, symptoms begin on one side of the body and migrate over time to the other side.

There is no test (such as a blood test, brain scan or EEG) to make a diagnosis of PD. Instead, a doctor takes a careful medical history and performs a thorough neurological examination, looking in particular for two or more of the cardinal signs to be present. Frequently, the doctor will also look for responsiveness to Parkinson's medications as further evidence that Parkinson's is the correct diagnosis.

Unfortunately, because there is no definitive test for Parkinson's disease and because PD's symptoms are similar to those of other neurological conditions, the misdiagnosis rate is significant. It is worthwhile to consider a second opinion and to reach out to a neurologist with specific expertise in movement disorders.

What else could it be?
Early in the disease process it may be difficult to know whether symptoms indicate Parkinson's disease or a syndrome that mimics it. Some conditions that could potentially be mistaken for Parkinson's include:

Medication-induced parkinsonism. Medications frequently associated with the development of parkinsonism are those often prescribed as anti-psychotics or for major depression. Sometimes anti-nausea medications can also cause parkinsonism. Unlike Parkinson's, symptoms typically occur on both sides of the body simultaneously. These symptoms usually resolve within weeks or months of discontinuing the medication.

Essential tremor. Essential tremor is considered the most common neurologic movement disorder. It is a chronic condition characterized by involuntary, rhythmic tremor of a body part, most typically the hands and arms, especially when they are being used for activities such as writing or eating.

Progressive Supranuclear Palsy (PSP). Early onset of imbalance, frequent falls, rigidity of the trunk, and (eventually) eye-movement problems characterize PSP. Symptoms usually begin after age 50 and progress more rapidly than with Parkinson disease.

Normal Pressure Hydrocephalus (NPH). NPH is distinguished by a trio of symptoms: gait problems, urinary incontinence and dementia. Experienced movement-disorder neurologists can generally distinguish NPH from PD quite easily. Occasionally, a brain scan may be useful.

What causes Parkinson's disease?
The exact cause of Parkinson's disease is unknown, although research points to a combination of genetic and environmental factors. If a continuum existed, with exclusively genetic causes at one end and exclusively environmental causes at the other, different patients would likely fall at many different places along that continuum.

In the past 10 years, researchers have identified a number of rare instances where Parkinson's disease appears to be caused by a single genetic mutation. In these cases, the mutated gene is passed from generation to generation, resulting in a great number of Parkinson's cases within an extended family. On the opposite of end of the continuum, in the early 1980s, a group of heroin users in California took drugs from a batch contaminated with a substance called MPTP. After ingesting this chemical, the drug users were stricken with a form of Parkinson's disease that was primarily, if not exclusively, "environmental" in origin.

For most Parkinson's patients, the cause lies somewhere in the middle. While many PD patients report one or more family members with the disease, it is not always clear that one or several genes are the cause. Similarly, while some patients suspect that exposure to one or another chemical or environmental toxin caused their PD, this also cannot be conclusively proved. Scientists currently believe that, in the majority of cases, genetic and environmental factors interact to cause Parkinson's disease. Research into this subject continues aggressively every day. Unfortunately, however, it is generally impossible to determine what specifically caused an individual's PD.

What are the risk factors for PD? Is there anything that can be done to reduce risk?
Because the causes of PD are not known, there is currently no scientifically validated preventive course to reduce the risk of Parkinson's onset. The single biggest risk factor for PD is advancing age. Men have a somewhat higher risk compared to women.

That being said, a number of studies have highlighted factors that are associated with either greater or lesser risk of Parkinson's disease. While these studies do not definitively link these factors with Parkinson's disease one way or another, they are subjects on which further research is needed. For example, smoking and caffeine consumption have been associated with lower rates of Parkinson's disease, while head injury and pesticide exposure have been associated with higher risk. One thing is clear: more research remains to be done.

What drugs or other treatments can stop Parkinson's from getting worse over time?
While the ultimate therapeutic goal for PD is a "neuroprotective" treatment that would halt the progression of the disease or a "neuroregenerative" treatment that would rejuvenate sick nerve cells, no such treatment exists today. Available treatments offer only symptomatic relief. Nevertheless, significant research is being performed in the pursuit of "disease-modifying" therapies, and recent scientific discoveries have increased optimism that such therapies will be developed.

What drugs are used to treat Parkinson's disease and how do they work?
While none is without side effects, available drugs can greatly enhance the life of a Parkinson's patient, sometimes restoring function to nearly normal for some period of time. Over time, as the disease progresses, drug dosing is adjusted to best meet a patient's symptomatic needs.

Every person living with Parkinson's disease experiences a different range of symptoms. For this reason, not all treatments are of equal value to all patients. It's essential to work closely with your doctor and all medical caregivers involved with your treatment regimen to develop the approach that's right for you. Decisions about which treatments to use, how long they can be expected to remain beneficial, and when to begin are highly individualized in PD. The table below offers an overview of some of the most commonly prescribed medications used to treat Parkinson's.

Drugs Used to Treat Parkinson's

Dopamine Replacement Therapies (Examples: Levodopa/Carbidopa)

About	Pros	Cons and Complications
In the 1970s, Levodopa was the first drug approved specifically for Parkinson's. Levodopa is converted by enzymes in the brain to produce dopamine, thereby supplementing function that has been lost as dopamine-producing neurons die. Levodopa is most frequently combined with Carbidopa to slow enzyme break down of Levodopa before it reaches the brain. In the United States, this Levodopa/ Carbidopa combination may be sold under the brand name Sinemet. Sinemet is available in both standard release and controlled release preparations.	In most patients, Levodopa/Carbidopa significantly improves mobility and allows them to function relatively normally, at least in the early stages of the disease. Because Parkinson's worsens over time, increased doses must be taken to manage symptoms as they progress. Levodopa/Carbidopa is widely recognized as the most effective treatment for motor symptoms of the disease.	Levodopa/Carbidopa has not been shown to slow disease progression. Additionally, the drug has significant side effects for some patients, including dyskinesia (involuntary movements and tics), hallucinations and illusions. Over time, symptoms may begin to come back before it is time for another dose of Levodopa/Carbidopa. This change in symptoms is called "wearing-off." As "wearing-off" becomes more noticeable, the duration of good response to Levodopa/Carbidopa (known as "on" time) shortens, while the duration of poor response (known as "off" time) may lengthen. High protein-diets may inhibit Levodopa/Carbidopa absorption in some people, thus impacting drug effectiveness. Not effective at treating all symptoms of PD. Posture, depression and cognitive problems are not responsive to Levodopa-Carbidopa.

Dopamine Agonists (Example: Pramipexole, Ropinerole, Bromocriptine)

About	Pros	Cons and Complications
Dopamine agonists are drugs that do not convert to dopamine in the brain, but instead mimic the effect of dopamine on the brain. Dopamine agonists supplement function that has been lost as dopamine-producing neurons die. While some dopamine agonists have been around for years, new dopamine agonists have been developed that attempt to better manage side effects. Dopamine agonists can be used alone or in combination with Levodopa/Carbidopa.	Dopamine agonists cause motor fluctuations including dyskinesias less frequently than Levodopa/Carbidopa. No protein effects as seen with Levodopa/Carbidopa. Agonists offer potential for alternate forms of delivery (such as a skin patch) that may offer certain advantages over oral administration.	Dopamine agonists have not been shown to slow the progression of the disease. Dopamine agonists are not as effective as Levodopa/Carbidopa for the treatment of motor symptoms. They may also cause other side effects including daytime sleepiness, sudden unanticipated sleep ("sleep attacks"), hallucinations and risk-taking behavior-such as gambling and sexual obsessions. Not effective at treating all symptoms of PD. Posture, depression and cognitive problems are not responsive to dopamine agonists.

MAO-inhibitors (Brand names: Selegiline, Rasagilene)

About	Pros	Cons and Complications
MAO-inhibitors inhibit an enzyme that breaks down Levodopa, thus extending its action. Used alone or in combination with Levodopa/Carbidopa.	Can prolong the action of Levodopa. May have a mild antidepressant effect Research is ongoing, but these drugs may offer some neuroprotection.	Small symptomatic benefits. The drugs may have interactions with other medications and foods: • Blood pressure issues must be monitored carefully • Both have potential interactions with antidepressants • Selegiline has more problems in the elderly (especially hallucinations).

COMT-inhibitors (Examples: Entacapone, Tolcapone)

About	Pros	Cons and Complications
Catechol O-methyltransferase (COMT) inhibitors allow a larger amount of Levodopa to reach the brain, thus raising dopamine levels there. They help provide a more stable, constant supply of Levodopa, which makes its beneficial effects last longer and manage off times better. Used in conjunction with Levodopa/Carbidopa	Can prolong the action of Levodopa.	By increasing the amount of Levodopa that reaches the brain, a COMT inhibitor also may increase some of the side effects associated with Levodopa use, including dyskinesia and hallucinations. Tolcapone has had some liver issues in some patients.

Other Pharmacological Approaches (used in conjunction with Levodopa/Carbidopa and dopamine agonists)

About	Pros	Cons and Complications
Amantadine reduces symptoms of fatigue, tremor, and bradykinesia in early Parkinson's disease and may reduce dyskinesias in more advanced PD. Anti-cholinergics may be useful in treating people younger than 70 whose main symptom is tremor. People with slowness, stiffness, and balance problems, and people without tremor usually do not benefit from these medications. They also may be useful in controlling drooling.		Side effects of Amantadine may include drowsiness and hallucinations. Potential side effects of anticholinergics include memory and cognition problems, hallucinations, constipation, dry mouth, and difficulty initiating urination. Anticholinergics usually are not used in people older than 70 or people who have developed mental impairment, such as memory problems, because these people are more likely to have severe side effects such as confusion and hallucinations.

Are there effective surgeries for Parkinson's disease?
Similar to available pharmacological treatments, no currently available surgical treatment has been proven to either slow down the disease or "rejuvenate" the sick and dying nerve cells affected by PD. Today's PD surgeries offer only symptomatic benefits.

Because of the level of risk inherent in any brain surgery, it is usually an option only for patients with severe or quickly debilitating Parkinson's disease or those with severe medication-induced side effects, such as debilitating dyskinesias. The decision about whether or not to undergo surgery should be made in consultation with the physicians and caregivers involved in a patient's treatment regimen and, of course, identifying an experienced surgical team is essential.

Deep Brain Stimulation
Today, the most commonly discussed surgical treatment is deep brain stimulation (DBS), a procedure that seeks to reduce "on/off" fluctuations as well as dyskinesias. While we do not understand how DBS works, it seems to counteract the abnormal neuronal functioning that occurs in PD. DBS is increasingly attractive for many advanced Parkinson's patients, particularly as more surgeons become proficient with the technique.

DBS is not well-suited for all patients. Generally, patients with typical PD who have had a good response to levodopa, but who are experiencing medication-related motor side effects, such as dyskinesias may be good candidates. DBS is usually not recommended for patients with dementia.

In DBS, a very thin electrode (about the diameter of a piece of spaghetti) is implanted into the brain, targeting motor circuits that are not functioning properly. Small electrical pulses from a device similar to a cardiac pacemaker are then used to stimulate a small brain region and block the signals that cause some Parkinson's symptoms. DBS may be targeted to the globus pallidus or subthalamic nucleus to improve motor function. The stimulator can be adjusted as necessary to optimize its effects.

Generally, DBS does not improve those symptoms that do not respond to levodopa. DBS may help patients achieve motor function off of medication that is similar to their best pre-operative motor function while on medication, although this is not always the case. DBS also reduces motor fluctuations and off-time. While DBS

can produce major improvements in many aspects of PD, this is not always the case. It is important to approach DBS with realistic expectations and an acceptance of the risks and benefits associated with surgery.

Other Surgical Approaches
Because deep brain stimulation has increasingly become the surgical method of choice where it is available, other older surgeries-such as pallidotomies and thalatomies-are used less often than they used to be. Both of these approaches lesion the brain-in effect putting small holes in the brain-to achieve outcomes, and these lesions are not reversible.

What sorts of non-pharmacological treatments should be considered?
Non-pharmacological treatments are important for many patients. Such treatments can not only help to relieve some of the motor symptoms of Parkinson's disease, but can aid in the management of postural instability and non-motor symptoms as well. Determining which non-drug treatments may best address and treat your Parkinson's disease should be done in consultation with the physicians and other caregivers involved in your overall treatment plan.

Exercise. Given what we know about the universal health benefits of exercise, it is not surprising that exercise and physical therapy are the most frequently suggested non-pharmacological treatments for Parkinson's disease. Exercise programs can help people with Parkinson's stay active and relatively limber, and improve balance and motor coordination. Some doctors also prescribe physical therapy or muscle-strengthening exercises.

Exercise may have effects on some of the non-motor symptoms of Parkinson's as well. For example, exercise can reduce sleep dysfunction and can improve overall emotional well-being.

Speech Therapy. Parkinson's can bring on problems with speech, including reduced or fading volume, vocal clarity issues, and reduced or increased pace of speaking. Speech therapy is increasingly viewed as an intervention that can greatly enhance speech and overall quality of life. Lee Silverman Voice Treatment (LSVT) is the program most frequently recommended.

Occupational Therapy. Occupational therapists seek to help people with Parkinson's in a variety of tasks that impact daily living and quality of life, from physical movement to handwriting to adaptation of utensils and other household items.

Psychological Therapy/Counseling. Depression and anxiety can be intrinsic symptoms of Parkinson's disease-much like rigidity or tremor. Left untreated, these symptoms can significantly diminish a person's quality of life and overall health. In addition to pharmacological treatments, psychological therapy and counseling can be helpful.

What therapies are currently in development?
A great deal of research is being conducted on new treatments to (1) improve the symptoms of PD; (2) protect or restore the nerve cells affected by PD-and thereby slow down disease progression; (3) prevent or suppress dyskinesias; and (4) improve non-motor symptoms, such as depression or cognitive impairment.

The Foundation frequently receives questions about the following therapies in development:

Neurotrophic Factors
Some of the most interesting recent clinical trials have examined neurotrophic factors for the treatment of Parkinson's disease. In preclinical (non-human) studies, the neurotrophic factors GDNF and neurturin have shown both symptomatic and neuroprotective benefits. This promising preclinical work makes neurotrophic factors one of the most exciting current areas of research.

The challenge for clinical use of neurotrophic factors is delivering them effectively to the brain. Pump infusion of GDNF was used in two small unblinded clinical trials, with positive results, but the results were not replicated in a more recent blinded clinical trial. Currently, a neurturin gene therapy safety trial has been completed and a larger trial is planned to examine its clinical efficacy.

For more information on neurotrophic factors, see the MJFF Viewpoints section.

NET-PD (Neuroprotection Exploratory Clinical Trials) Program
The National Institute for Neurological Disorders and Stroke (NINDS) has conducted several trials to explore the effectiveness of certain compounds that have shown potential to slow the progression of Parkinson's disease in non-human preclinical studies. To date, tests have been done on CoQ10, a substance widely used as a dietary supplement that may have neuroprotective effects, and GPI-1485, an investigational drug that may have a regenerative effect. A second study looking at minocycline, an antibiotic with anti-inflammatory effects, and creatine, a compound that may help maintain healthy mitochondrial function and thus counteract the possible role of oxidative stress in Parkinson's disease, has also been completed. These studies were futility trials-designed to show which compounds should be further pursued and which should not. To date, only the creatine and minocycline trials have been published, with this data concluding that further studies should be done. A large trial of creatine is scheduled to begin in early 2007.

Cell Replacement Therapy
Cell replacement therapy is designed to replace the neurons that degenerate in PD. While there are a variety of potential sources of cells for this therapy, most work currently focuses on stem cells. A stem cell has the potential to differentiate into any cell type in the body. The premise of this approach is that stem cells in a dish can be coaxed to become healthy dopamine neurons, which can then be transplanted into the brain to replace the sick and dying neurons in Parkinson's disease.

While U.S. government restrictions on embryonic stem cell research have undoubtedly slowed the pace of this work in recent years, some key insights have emerged. These findings, however, have highlighted the complexity of cell replacement, and have made it clear that significant basic research remains to be done before stem cell replacement therapy is a viable option for clinical trials.

For more information on cell replacement therapy, see the MJFF Viewpoints section.

How can I become involved in clinical trials to speed the development of new therapies?
The Michael J. Fox Foundation, together with seven leading Parkinson's groups and the National Institute of Neurological Disorders and Stroke, is leading a nationwide effort to accelerate the development of new treatments for Parkinson's disease by increasing awareness and participation in clinical research. To learn about the importance of clinical trials and to find trials in your area, contact the information request line for PDTrials at (888) 823-8889 or visit www.PDtrials.org.

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